ZINC SALTS
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I 39

MONOGRAPH

ON

ZINC SALTS

VOLUME I

Including

Zinc Gluconate
Zinc Cholride
Zinc Oxide
Zinc Stearate
Zinc Sulfate
Zinc Acetate
Zinc Carbonate

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Table of Contents

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Summary

Zinc and its salts have been the subjects of intensive biochemical investigations since the 1920's when the essential nature of zinc for man was elucidated. Recent studies in which radioisotopic techniques have been utilized have given us a rather thorough knowledge of the metabolism, excretion, and general biochemical activity of zinc and its several salts in selected organisms. Despite this, there are unresolved questions on the effects of zinc on animals - specific oral toxicity levels and carcinogenicity, for example.

In the human body, zinc has been reported by Forbes to be absorbed through the walls of the small intestine (193). Van Campen and Mitchell specified further that the actual absorption occurred in the duodenum (593). Several workers have found zinc to be more readily available from diets containing animal protein than from diets containing plant protein because of the occurence of phytic acid in the latter(422, 423, 367). Phytic acid makes zinc less available to the organism as a consequence of its chelating (or complexing) activity.

Drinker, et al., in early investigations suggested that zinc compounds ingested are converted to zinc chloride and zinc lactate in the stomach (142). They further suggest that zinc forms a protein complex with enzymes in the stomach, and these complexes are either soluble or dissolved by the free HCl present (143). This mechanism has never been confirmed.

Feaster, et al., reported that 8% of the ingested zinc is absorbed within 48 hours (181). Drinker, et al., thought that the bulk of absorbed zinc was excreted directly into the intestinal tract (some via the bile from the liver and some from the pancreatic secretions) and eventually was excreted via the feces (142). Only a small fraction of absorbed zinc was in the urine (143). Zinc is accumulated in the body to some extent, the highest zinc concentrations being found in those organs involved in the excretion of zinc (142, 143, 181). Richmond, et al., reported on the basis of tests performed with four individuals that the average effective biological half-life of ^{65}Zn is 154 days (468).

Sutton and Nelson reported that the administration of zinc as either the chloride or the sulfate increased the blood sugar level of fasting rats (568). Zinc has also been implicated in the accumulation of Mg^{++} (64) and K^{+} (65) by heart mitochondria. Sadasivan observed that the retention of N, P, and S is decreased and the urinary excretion of creatinine and uric acid increased after zinc ingestion by test rats (494, 498). He also reported that zinc ingestion resulted in a decrease in liver weight and fat content (496). Zinc reduced the dry weight and ash content of bones and interfered with bone development and mineralization (496).

Several scientists have reported that zinc ingestion may result in a microcytic, hypochromic anemia (122, 147, 218, 236, 518, 537). This effect has been attributed to either reduced iron levels (121) or reduced copper levels (218).

Zinc excess affects the metabolism of Ca, Cu, Fe, and P; on the other hand, excessive dietary levels of these elements affect the metabolism of zinc (77, 121, 122, 123, 218, 358, 554). Settlemire and Matrone correlated the anemia in zinc-fed rats with ^{59}Fe excretion and postulated that the reduction in body Fe results from an increased turnover of red blood cells (518). In muscle tissue, varying concentrations of zinc may stimulate or inhibit ATPase activity of myosin (57, 88, 208, 642). In vitro studies by Edman have revealed that zinc in the presence of ATP induces relaxation of muscle fiber bundles (glycerol-extracted) (154, 155, 156).

Zinc acts as a coenzyme or is an integral component of a number of metalloenzymes; zinc is an essential element for activation of these enzymes. Deoxyribonuclease (393) and intestinal phosphatases (110, 270) are affected in this manner. Conversely, a large number of enzymes have been found to be inhibited or denatured by zinc. Those discussed in the literature include catalase, cytochrome oxidase, alkaline beta-glycerophosphatase, pyrophosphatase, orthophosphatase, succinic dehydrogenase, phosphoglucomutase, plasmin, prolidase, xanthine oxidase, and ceruloplasmin (110, 122, 123, 147, 270, 324, 358, 405, 455, 480, 567, 595).

Sahyun reported that high levels of zinc augmented insulin (499). Scott and Fisher and Drinker, et al., observed fibrotic changes in the pancreas of cats on high-zinc diets (515, 142).

Schapiro, et al., found zinc sulfate to be an effective emetic (508).

Recently, Gusswein has reported that rats fed zinc as the acetate exhibit particular resistance to respiratory infections (206).

There have been numerous feeding studies conducted with zinc compounds on a variety of test animals. As a result of the essential nature of zinc for man, many (if not most) of these feeding studies are involved with necessary requirement dietary levels. Therefore, it is rather meaningless to include every feeding study. As a consequence, only those studies designed to study toxicity or toxic levels of zinc salts or those in which toxic or detrimental effects attributable to zinc are reported will be examined.

Because of the relatively large number of studies, animals tested, and zinc salts under consideration, it has been felt that perhaps the most facilitative reporting of the literature would involve examining studies of each zinc salt upon the same species of test animals. The following report assesses the toxic effects/levels of zinc acetate, carbonate, chloride, oxide, and sulfate on appropriate test subjects.

Boyland and Roe reported in 1963 on a long-term study then in-progress in which zinc as zinc sulfate was included at a level of 500 or 1000 ppm in the drinking water of test mice. After a period of over a year, no evidence of carcinogenicity of zinc ion (as the sulfate) was observed (60).

Haime reported that zinc (as zinc chloride) at a dosage of 10-20 mg/l resulted in an increased incidence of carcinomas in tumor-resistant mice (239).

Zinc levels of 5-20 mg Zn/l, as zinc chloride, were found by De Szilvay to produce a significant increase in the tumor frequency of mice (137).

There have been 5 papers concerning the effects of zinc salts on chicks. Klussendorf and Pensack reported that zinc fed to chicks as zinc acetate at a zinc level of 125 mg/kg/day for an indefinite period did not affect growth; however, zinc at the 250 mg/kg/day level for the same unspecified period resulted in a slight growth depression (306). Roberson and Schaible, however, found that zinc (given as zinc sulfate) at a level of 125 mg/kg/day for 4 weeks in the diet resulted in a slight growth depression; at a level of 188 mg/kg/day for the same period, zinc definitely depressed the growth of chicks (476). Tahara, et al., found that zinc (as zinc sulfate) included in the diet of chicks at a level of 250 mg/kg/day for 26 days resulted in the definite growth depression and anemia of test subjects (572). Roberson and Schaible also studied the effect of zinc as zinc carbonate and found that a zinc level of 188 mg/kg/day for 4 weeks depressed growth of chicks; at the 375 mg/kg/day level, zinc caused mortalities in one-third of the chicks (476). Klussendorf and Pensack found that zinc (as zinc carbonate) at a level of 250 mg/kg/day for 71 days in the diet caused a slight growth depression (306). At a level of 250 mg/kg/day for 26 days, zinc (as zinc carbonate) was shown by Tahara, et al., to cause growth depression; at a level of 375 mg/kg/day an increase in mortality was effected (572). Roberson and Schaible reported no toxic effects attributable to zinc when fed (as zinc oxide) at a level of 125 mg/kg/day for 5 weeks to chicks; however, at a level of 188 mg/kg/day for 4 weeks, zinc depressed growth (and was considered by Roberson and Schaible to be MTD at this level) (476). Johnson, et al., reported a slight growth depression attributable to zinc (as zinc oxide) at a level of 247 mg/kg/day for 10-16 weeks (288). Tahara, et al., found that zinc (as zinc oxide) fed at a level of 375 mg/kg/day for 26 days resulted in a slight depression of food intake but no other detrimental effects (572). Mehring, et al., observed no toxic effects attributable to zinc (as zinc oxide) at a dietary level of 103 mg/kg/day for 9 weeks (374).

An additional difficulty is encountered in feeding studies involving rats. The included levels of the compound in the diet may be given as ppm (or mg/kg) of the compound or of zinc given as the compound. Gesswein fed rats an average of 1000 mg of zinc acetate/kg/day for 52 weeks and found that this level of zinc acetate resulted in growth depression and toxic manifestations that were resolved over the period of regimen; at the 2000 mg/kg/day level, zinc acetate caused mortalities among test rats within 2 weeks (206). Salant fed zinc acetate at a level of 50-105 mg/kg/day for 4 months to rats and found that renal function of the animals was abnormal (500). Thompson, et al., over a period of 29 weeks fed 2-38 mg of zinc (as zinc acetate)/day to pregnant rats and found that the health of the parent animal and offspring were apparently unaffected at this level (580). Heller and Burke fed zinc (as zinc carbonate) at a level of 250 mg/kg/day for 3 generations (about 1 year/animal) and reported that there seemed to be no untoward effects (248). Sutton and Nelson fed zinc (as zinc carbonate) to test rats for 39 weeks at a level of 500 mg/kg/day; these animals exhibited a marked anemia, and the females failed to become pregnant (568). Over a 4-6 week period, Smith and Larson fed zinc (as zinc carbonate) at levels of 700 and 1000 mg/kg/day. At the 700 mg/kg/day level, growth depression resulted and at the 1000 mg/kg/day level, severe mortality resulted (537). Gross, et al., fed zinc chloride to rats at a level of approximately 1000 mg/kd/day for 35 weeks and found that a pantothenic acid deficiency resulted within 9 weeks (224). Wilkins dosed rats with zinc chloride for 15 months at levels of 300 and 600 mg/kg/day and found no toxic effects apparent; however, at a level of 3000 mg/kg/day, zinc chloride resulted in a 50% mortality and severe growth retardation for test rats (626). Heller and

Burke fed zinc chloride at 250 and 500 mg/kg/day levels to rats for about a year and over 3 generations. At the 250 mg/kg/day level, zinc chloride exerted no apparent toxic effect; at the 500 mg/kg/day level, on the other hand, increased incidence of stillbirths were effected (248). Zinc as zinc oxide fed to 3 generations of rats over a period of several years by Heller and Burke resulted in no untoward effects at a zinc level of 500 mg/kg/day (248). Cox, et al., reported that zinc (as zinc oxide) fed to pregnant rats at a level of 200 mg/kg/day for 16-21 days resulted in a lowered fetal dry weight and a decreased hemoglobin level in the test rats (122). Thompson, et al., found that zinc (as zinc oxide) at a dosage of 6.5-38 mg/rat/day resulted in no toxic effects (580). Drinker, et al., reported no toxic effect from zinc (as zinc oxide) at daily levels of 34.4 mg over a period of 35-36 weeks (143). Kim and Rosenthal found that zinc (as zinc sulfate) fed to rats at a level of 20-40 mg/kg/day for 10 days had no obvious effect (298). Kulwich, et al., determined that, at a level of about 100 mg/kg/day for 14 weeks, zinc sulfate resulted in increased hepatic-Zn but no other effects (323). Hagan, et al., found that zinc sulfate fed to rats at a level of 4-6 mg/kg/day for 77 weeks resulted in pathogenic blood changes, and that, at levels of about 35-40 mg/kg/day for 17 months, microcytosis and poly- and hyperchromasia resulted (236). Heller and Burke fed rats zinc (as zinc sulfate) for over a year and for 3 generations at a level of 250 mg/kg/day; they found no untoward effects (248). Dutt and Vasudevan in a progress report commented that rats fed 100, 150, and 200 mg/kg/day of zinc source for an unreported period exhibited hyperkeratosis of the gastric mucosa and foci of hepatic degeneration upon histopathological examination (150).

Cherkasova reported that zinc enhanced the viability of rats injected with Pliss lymphosarcoma, and that these rats were more refractory to subsequent development of lymphosarcomas when they were fed zinc (as the chloride) (107).

Drinker, et al., fed zinc (as zinc oxide) to cats at a level of 50 mg/kg/day for 31 weeks and reported no toxic effects. Over a period of 13 weeks at a level of 223 mg/kg/day, zinc (as zinc oxide) resulted in fibrous changes in the pancreas (142).

Drinker, et al., fed dogs zinc (as zinc oxide) at levels of 36 mg/kg/day for 19 weeks and 76.5 mg/kg/day for 15 weeks without realizing any toxic manifestations from the regimen (142). Hagan, et al., found that dogs fed zinc sulfate at 200 mg/kg/day for 7 weeks became violently ill (nauseated) and vomited consistently; at levels of 100 mg/kg/day for 32 weeks, zinc sulfate caused vomiting in dogs by 32nd week and a hyperplastic bone marrow (236).

Ott, et al., fed zinc (as zinc oxide) to sheep for 10 weeks at a level of 60 or 80 mg/kg/day. At the 60 mg/kg level, sheep exhibited growth depression; at the 80 mg/kg level, mortality increased (432). James, et al., found that zinc sulfate fed to sheep at a level of 5 mg/kg/day for 147-152 days resulted in a higher hepatic-Zn level (283).

Brink, et al., fed zinc (as zinc carbonate) to swine for 42, 36, or 33 days at respective levels of 40, 80, and 160 mg/kg/day. The 40 mg/kg/day level had no effect; the 80 mg/kg/day level depressed growth; and, the 160 mg/kg/day level resulted in a 50% mortality (66). Kulwich, et al., fed zinc sulfate at a 40 mg/kg/day level to swine for 27 weeks without toxic effects (323). Milosavljevic fed zinc sulfate to swine at a level of 8 mg/kg/day for 3.5 months, and the swine showed depressed growth and food intake (390).

Ott, et al., fed zinc (as zinc oxide) to cattle for 71 days at a level of 39 mg/kg/day and found this to be the toxic threshold for zinc. For the same period of time at a level of 51 mg/kg/day, zinc caused severe growth depression in cattle (434).

Brewer, et al. (63); Pories, et al. (454); Husain (275); Cohen (114); and Carruthers (87) all fed zinc sulfate to individuals for periods of 32-120 days without resulting in toxic effects.

ZINC GLUCONATE

Chemical Information

I. Nomenclature

A. Common Name
Zinc Gluconate

B. Chemical Name
Zinc Gluconate

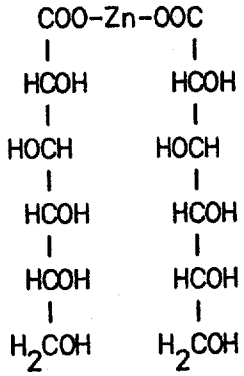
C. Trade Names
None

D. Chemical Abstracts Service Registry No.
004468024

II. Empirical Formula

$(C_6H_{11}O_7)_2Zn$

III. Structural Formula



IV. Molecular Weight

457.69

V. Specifications

Not available

VI. Description

Not available

VII. Analytical Methods

See zinc salts

VIII. Occurrence

See zinc salts

ZINC CHLORIDE

Chemical Information

I. Nomenclature

A. Common Names
Zinc Chloride
Butter of Zinc

B. Chemical Name
Zinc Chloride

C. Trade Name
None

D. Chemical Abstract Service Registry No.
007646857

II. Empirical Formula

$ZnCl_2$

III. Structural Formula

$ZnCl_2$

IV. Molecular Weight

136.29

ZINC OXIDE

Chemical Information

I. Nomenclature

A. Common Names
1. Flowers of zinc
2. Zinc white
3. Chinese white
4. Philosopher's wool

B. Chemical Name
Zinc Oxide

C. Trade Name
Zinclte

D. Chemical Asbtracts Service Registry No.
001314132

II. Empirical Formula
ZnO

III. Structural Formula
ZnO

IV. Molecular Weight

81.38

V. Specifications

Chemical - A.C.S

Assay (ZnO)	99.0%
Insoluble in H_2SO_4	0.010%
Alkalinity	passes A.C.S. test
Chloride (Cl)	0.0005%
Nitrate (NO_3)	0.003%
Sulfur compounds (as SO_4)	0.005%
Arsenic (As)	0.0001%
Iron (Fe)	0.0005%
Lead (Pb)	0.005%
Manganese (Mn)	0.0005%
Substances not precipitated by $(NH_4)_2S$ (as SO_4)	0.10%

VI. Description

A. General Characteristics.

Zinc oxide is a white or yellowish-white, amorphous powder having no distinguishable odor or taste.

B. Physical Properties

Melting point is greater than 1800 degrees centigrade
Density 5.47
Sublimes at normal pressure at 1800 deg C
Refractive index 2.0041, 2.02003
The pH of American process zinc oxide is pH 6.95 while
The French process zinc oxide has a pH of 7.37.

Zinc oxide is virtually insoluble in water (0.00016 gm/100 ml) H_2O at 29°C). It is soluble in dilute acetic or mineral acids, in ammonia, ammonium carbonate, and fixed alkali hydroxide solutions.

VII. Analytical Methods

See zinc salts

VIII. Occurrence

Zinc oxide is prepared by vaporization of metallic zinc by indirect heating in the presence of carbon monoxide gas and oxidation of the vapors with preheated air. It is also prepared from zinc ore known as franklinite or from zinc sulfide called zinc blende.

ZINC STEARATE

Chemical Information

I. Nomenclature

A. Common Name
Zinc Stearate

B. Chemical Name
Zinc Stearate

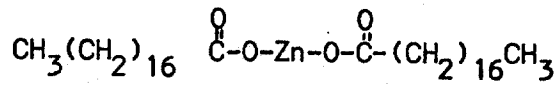
C. Trade Name
None

D. Chemical Abstract Service Registry No.
000557051

II. Empirical Formula

$Zn(C_{18}H_{35}O_2)_2$

III. Structural Formula



IV. Molecular Weight

632.30

V. Specifications

Chemical - U.S.P. Zinc Stearate corresponding to	not less than 13% ZnO and not more than 15% ZnO
pH	neutral
Alkali or alkaline earth metals as sulfate	not more than 10 mg/g
Fatty acid solidification temp. (titer)	not below 54°C

VI. Description

A. General Characteristics

Zinc stearate is a fine, soft, bulky, white powder having a slight characteristic odor.

B. Physical Properties

Melting Point	130°C
Flash Point	530°C
Autoignition Temperature	790°F

Zinc stearate is hydrophobic and is thus insoluble in water. It is also insoluble in alcohol and ether. Zinc stearate is soluble in benzene and decomposes in dilute acids.

VII. Analytical Methods

See zinc salts

VIII. Occurrence

Zinc stearate is prepared from stearic acid and zinc chloride.

ZINC SULFATE

Chemical Information

I. Nomenclature

A. Common Names
1. Zinc Sulfate
2. White Vitreol
3. Zinc Vitreol

B. Chemical Name
Zinc Sulfate

C. Trade Name
Zinkosite

D. Chemical Abstracts Service Registry No.
(anhydrous) 007733020
(monohydrate) 007446197

II. Empirical Formula

$ZnSO_4$

III. Structural Formula

$ZnSO_4$

IV. Molecular Weight

161.44 (anhydrous)
179.46 ($ZnSO_4 \cdot H_2O$)
269.54 ($ZnSO_4 \cdot 6H_2O$)
287.55 ($ZnSO_4 \cdot 7H_2O$)

V. Specifications

A. Chemical (A.C.S.)

Assay ($ZnSO_4 \cdot 7H_2O$)	99.0-102.0%
Insoluble Matter	0.005%
pH of 5% Solution at 25°C	4.4-6.0
Chloride (Cl)	0.0005%
Nitrate (NO_3)	0.002%
Ammonium (NH_4)	0.001%
Arsenic (As)	0.00005%
Lead (Pb)	0.002%
Manganese (Mn)	0.0002%
Substances not precipitated by $(NH_4)_2S$ (as SO_4)	0.20%

B. Food

C. Food Chemicals Codex

Assay	99.0-108.7%
Acidity	Passes test
Limits of Impurities	
Alkalies	Not more than 0.5%
Alkaline earths	Not more than 0.5%
Arsenic (as As)	Not more than 3 ppm (0.0003%)
Heavy metals (as Pb)	Not more than 10 ppm (0.001%)
Selenium	Not more than 30 ppm (0.003%)

VI. Description

A. General Characteristics

Anhydrous - white rhombic crystals
Monohydrate - powder or granules
Hexahydrate - monoclinic crystals
Heptahydrate - odorless crystals or granules or powder having an astringent taste. It is efflorescent in dry air.

B. Physical Properties

Anhydrous zinc sulfate decomposes at 740°C. It is soluble in water (42 g/100 ml at 0°C and 61 g/100 ml at 100°C). It is also slightly soluble in alcohol and soluble in glycerol.

The monohydrate loses water at about 238°. It is soluble in water (89.5 g/100 ml at 100°C) and is practically insoluble in alcohol.

The hexahydrate loses 5 water molecules above 70°C. It is soluble in water and slightly soluble in alcohol.

The heptahydrate melts at about 50° when rapidly heated. At 100° it loses 6 H_2O molecules while at 200° it loses all of the water. The heptahydrate decomposes above 500°. One gram dissolves in 0.6 ml water and 2.5 ml of glycerol. It is insoluble in alcohol. An aqueous solution is acid to litmus having a pH of about 4.5.

C. Stability

Zinc sulfate should be kept in well closed containers.

ZINC ACETATE

Chemical Information

I. Nomenclature

A. Common Name
Zinc Acetate

B. Chemical Name
Zinc Acetate

C. No Trade Names

D. Chemical Abstracts Service Registry No.
000557346

II. Empirical Formula

$Zn(C_2H_3O_2)_2$ (Anhydrous)
$Zn(C_2H_3O_2)_2 \cdot 2H_2O$ (Dihydrate)

III. Structural Formula

$CH_3COOZnOOCCH_3$

IV. Molecular Weight

183.47 (Anhydrous)
219.50 (Dihydrate)

V. Specifications

Chemical - U.S.P. Zinc acetate	Not less than 82.74% or more than 87.32% zinc acetate and not less than 99% of hydrated zinc acetate ($Zn(C_2H_3O_2)_2 \cdot 2H_2O$)
Alkali or alkaline earth metals (as sulfate)	Not more than 10/mg/g
Arsenic	Passes test
Heavy metals	Not more than 50 ppm

VI. Description

A. General Characteristics

Zinc Acetate is in the form of crystalline plates or granules. It has a faint acetous odor and an astringent taste. It is slightly efflorescent.

B. Physical Properties

	Anhydrous	Dihydrate
Density	1.840	1.735
Melting Point	242	237

Anhydrous zinc acetate sublimes in a vacuum while the dihydrate loses water at 100°C.

C. Solubility Properties

One gram dissolves in 2.3 ml water, 1.6 ml boiling water, 30 ml alcohol, and 1 ml boiling alcohol.

The aqueous solution is neutral or slightly acid to litmus and has a pH between 5-6.

VII. Analytical Methods

See zinc salts

VIII. Occurrence

Zinc acetate is prepared from zinc nitrate and acetic anhydride.

ZINC CARBONATE

Chemical Information

I. Nomenclature

A. Common Name
Zinc Carbonate

B. Chemical Name
Zinc Carbonate

C. No Trade Name

D. Chemical Abstracts Service Registry No.
003486359

II. Empirical Formula

$ZnCO_3$ (zinc carbonate)

Zinc Carbonate Hydroxide is a carbonate of somewhat variable composition. It is approximately $5ZnO \cdot 2CO_3 \cdot 4H_2O$ and contains about 70% ZnO or 56% Zn.

III. Structural Formula

$ZnCO_3$

IV. Molecular Weight

125.4 ($ZnCO_3$)

V. Specifications

VI. Description

A. General Characteristics

Zinc carbonate is a white crystalline powder.

Zinc carbonate hydroxide is an odorless powder.

B. Physical Properties

	Zinc Carbonate
Melting Point	300°C (loses CO_2)
Density	4.42

Zinc carbonate is practically insoluble in water (0.001 gm/100 ml at 15°C).

Zinc carbonate hydroxide is insoluble in water and alcohol. It is soluble in dilute acids, ammonia and ammonium carbonate solutions.

VII. Analytical Methods

See zinc salts

VIII. Occurrence

Zinc carbonate occurs in nature as the minerals calamite and smithsonite.

Chemical Information

VII. Analytical Methods

There are several methods for analyzing zinc ion. Among these is the alternating current spark excitation method of the Association of Official Agricultural Chemicals. In this method an electric spark arc is used to produce an emission spectrum. For zinc, the spectral line at 3345 Angstroms is used for measurement. The log intensity ratios are proportional to ion concentrations. Thus, the concentration of a sample can be determined by comparing it to a standard curve (17).

Atomic absorption spectrometry with an oxidizing flame is extremely valuable. A standard curve is made and ion concentrations are found from the standard curve. The range of detectability is 0.5 micrograms/ml - 5 micrograms/ml (17).

A colorimetric determination method can be used for the determination of zincs in foods. The sample is oxidized by heating it with nitric and sulfuric acids. Interfering ions such as Pb, Cu, Cd, Bi, Sb, Sn, Hg and Ag are precipitated as Sulfides. Cobalt, and Nickel ions are extracted as metal complexes of alpha-nitroso-beta-naphthol and dimethylglyoxime respectively with chloroform. The zinc ion is extracted as zinc dithizonate with carbon tetrachloride and transferred to dilute HCl. After final extraction, the absorbance is measured at 540 millimicrons and the concentration determined from a standard curve. Solutions containing 0.2 mg/ml of Zn can be measured (17).

Neutron activation analysis is a highly sensitive (as little as .5 ppb can be detected) and accurate method for the determination of zincs in specimens. In this method a stable isotope, A, is converted by a neutron flux to the radioisotope B, which subsequently decays into a stable nuclide, C. The qualitative identification of A can be made from the disintegration constant and the energy of radiations emitted by B. For quantitative determination, the sample is usually compared to the standard. Care must be taken to avoid contamination and loss of the element. Often certain elements emit radiations which obscure the radiations of the trace element of interest. The major and important limitation of this method is its high cost (600).

Zinc can also be analyzed using x-ray fluorescence. Zeitz and Lee developed an x-ray apparatus which takes advantage of both dispersive and nondispersive x-ray analysis. While nondispersive analysis is more sensitive, much better resolution can be obtained using dispersive analysis. The method allows for direct determination of the zinc weight fraction in biological specimens and for exact absolute determinations of the zinc content in small specimens. It has a limit of detectability of about 4×10^{-9} gm. The precision of the method is equivalent to an error of 5% in the weight fraction of the element present at the level of 0.1 micrograms zinc in samples of the order of several hundred micrograms (639).

VIII. Occurrence and levels found in

A. Plants

Warren et al., found these results in various plants: (610)

Gymnosperms

Plant	Needle ppm	Tip or Bud ppm	Stem ppm
Douglas Fir (Pseudotsuga taxifolia)	24	25	40
Yellow or Ponderosa Pine (Pinus ponderosa)	34	31	33
Lodgepole Pine (Pinus contorta)	38	42	36
White Bark Pine (Pinus albiculus)	30	31	40
Engelmann Spruce (Picea Engelmanni)	40	45	60
Sitka Spruce (Picea sitchensis)	--	--	29
White Spruce (Picea glauca)	--	40	--
Western Red Cedar (Thuja plicata)	12	14	26
Rocky Mountain Juniper (Juniperoas scopulorum)	--	15	10
Dwarf Juniper (Juniperous eommanis)	--	17	15
Sargaent Hemlock or "Alaska Pine" (Tsuga heterophylla)	13	16	50
Nuttall Alpine Fir (Abies lasiocarpa)	30	32	45
Balsum Fir (Abies amabilis)	--	25	32

Angiosperms

	Leaves ppm	Young (1st year) stems ppm	Stems (2nd year) ppm
Willow (genus Salix)	120	120	80
Poplar or Trembling Aspen (Populus tremuloides)	120	94	60
Cottonwood (Populus trichocarpa)	130	80	66
Scub Birch (Betula grandulosa)	170	140	160
Silver or Western Birch (Betula papyrifera)	213	104	65
Green, Mountain, or Sitka Adler (Alnus sinuata)	34	27	25
Syringa or Mock Orange (Philadelphus Lewisii)	23	34	28
Choke Cherry (pranus Demissa)	26	40	17
Saskatoon (Amelanchier alnifolia)	31	39	28
Mountain Maple (Acer Glabrum)	31	30	15
Devils Club (Echinopanax horridus)	--	38	--
Wax Berry (Symphoricapos racemosus)	24	30	18
Sagebrush (Artemisia tridentata)	28	20	--
Sagebrush (Artemisia trifida)	35	27	--

Hemphill found the concentration of zinc in the dry leaves of various fruit trees:

Apple	10-40 ppm
Blueberry	10 ppm
Orange	25-50 ppm
Sweet Cherry	5-60 ppm

He noted that the normal level of zinc in plants ranges from 25-150 ppm. Factors such as season and soil content cause these values to fluctuate (250).

B. Zinc in Animal Tissues

The quantitative and qualitative aspects of the zinc content of animal tissues have been treated in detail. The zinc concentration in most of the soft tissues of the body approximates 25 ppm on the fresh basis, and except in the liver, is not appreciably changed by alteration of zinc intake. Considerably higher (100-400 ppm) concentrations of zinc are found in bone, hair and wool, and portions of the prostate and the eye. Human prostatic fluid contains 10 times the concentration of zinc as is found in the whole gland, a finding in agreement with histochemical demonstration of zinc concentration in the glandular epithelium. In the young, growing animal the zinc concentration in bone ash is a sensitive reflection of zinc absorption especially at suboptimal intake levels. It is apparent that zinc accumulates in cartilage at sites of calcification and, once deposited in the calcified tissue, is firmly bound. Analysis of human autopsy material did not reveal age changes in bone ash zinc nor did an experiment in which rats were fed a constant diet over more than a year. It was found that the shaft of the rat femur had a lower zinc concentration (330 ppm of ash) than the head of the femur (430 ppm).

The major portion of the zinc in whole blood is in the erythrocytes where it occurs mainly as a constituent of carbonic anhydrase. Species differences are apparent in blood zinc, but the relative distribution among blood components is similar. More data are available for man than for other species, and average values indicate 7-8, 1.1-1.3, and 12-18 mu-g of zinc per milliliter of whole blood, plasma, and erythrocytes, respectively. Leukocytes contain 3% of whole blood zinc, but each leukocyte contains 25 times as much zinc as each erythrocyte. Plasma zinc is in part protein bound.

The occurrence of zinc in skin and other epidermal structures has been of interest because of its concentration in hair, wool, and nails (100-200 ppm) and because of the marked histological aberration in the skin of zinc-deficient animals. Actually, the skin itself does not contain remarkable concentrations of zinc (20-60 ppm of dry tissue). The epidermis does, however, contain 3 times the concentration of zinc than the corium does (25 vs. 75 ppm).

Only fragmentary data are available on the zinc content of skeletal muscle. Large variation in zinc content of individual muscles of swine has been reported recently. Porcine trapezius muscle had 3 times the concentration of zinc and of myoglobin that was present in longissumus dorsi.

The unusual concentration of zinc in certain portions of the eye has attracted much attention and has been carefully documented. The choroid of carnivora and particulary the tapetum lucidum contains higher concentrations of zinc than any other animal organ; this amounts in some species to as much as 13% of the dry tissue. A significant amount of the zinc seems to be bound in a zinc-cysteine complex, but its function is not known.

The previously reported intracellular distribution of zinc in rat liver has been confirmed. With the data reported in terms of micrograms of zinc per milligram of nitrogen, the following distribution was found: nuclei, 0.77; mitochondria, 0.42; microsomes, 0.65; supernatant, 2.0; and reconstituted whole liver, 1.05. These findings are consistent with the view that the

majority of the known zinc-containing enzymes are in the supernatant fraction of the liver cell. On a percentage basis 18-28, 7-9, 11-16, and 54-58% of the total liver zinc is present, respectively, in nuclei, mitochondria, microsomes, and supernatant.

The zinc content of the pancreas and its endocrine and exocrine secretions has been of much interest since the finding that crystalline zinc insulin has certain advantages in treatment of diabetes over metal-free insulin.

Investigations have indicated that species variation in zinc content of milk is not large and that "mature" milk may be expected to contain 37.5 ppm whereas colostrum may contain 4 times this amount. In recent investigations mature cow's milk was found to contain 4.1 ppm and sow's milk 7.3 ppm.

An area of great interest in zinc metabolism is related to the possible role of the large amounts of zinc found in portions of the male reproductive tract and its secretions. The prostate gland in particular concentrates zinc, although there are wide variations between species in the distribution of this element in the gland. In the rat, for example, the dorsal prostate may contain 180 ppm of zinc on the fresh basis whereas ventral prostate contains less than one-tenth of this amount. On the other hand, in the human prostate no correlation could be found between zinc content and histologic features of the gland, although there was a 20-fold difference in zinc content of different areas of a given gland and a general increase in zinc content as samples were taken further from the bladder.

The high zinc content of testes and of spermatazoa has been well documented. Investigations have shown that sperm obtained from vas deferens and epididymis contain as much zinc as those from the total ejaculate, which shows that they are not dependent on the zinc-rich prostatic fluid for their zinc content (193).

Seven zinc metalloenzymes have been characterized thus far. These are carbonic anhydrase from bovine erythrocytes; the alcoholic dehydrogenase of yeast and equine liver; the glutamic dehydrogenase of bovine liver; and the lactic dehydrogenase of rabbit skelatal muscle. Evidence seems to indicate that there are additional pyridine nucleotide-dehydrogenase metallodehydrogenases, although lack of their characterization precludes their inclusion in Table I. Many other enzymes seem to be activated by zinc (592).

TABLE I

ZINC METALLOENZYMES OF KNOWN METAL CONTENT

Enzyme	Abbreviation	Molecular weight	Amount of metal (%)	Ratio of metal to protein (gm atom/mole)	Ratio of coenzyme* to protein (mole/mole)	Ratio of metal to coenzyme* (gm atom/mole)	Empirical formula
Carbonic anhydrase (bovine erythrocytes)	CAD	30,000	0.2-0.3	1 (? 2)	—	—	$[(CAD)Zn_{1-2}]$
Carboxypeptidase (bovine pancreas)	CPD	34,300	0.18	1	—	—	$[(CPD)Zn]$
Alcohol dehydrogenase (yeast)	YADH	150,000	0.18	4	4 (NAD)	1 Zn/NAD	$[(YADH)Zn_4](NAD)$
Alcohol dehydrogenase (equine liver)	LADH	73,000 (84,000)	0.18	2	2 (NAD)	1 Zn/NAD	$[(LADH)Zn_2](NAD)_2$
Glutamic dehydrogenase (bovine liver)	GDH	1,000,000	0.02-0.03	2-4	2-4 (NAD)	1 Zn/NAD	$[(GDH)Zn_{2-4}](NAD)_{2-4}$
Lactic dehydrogenase (rabbit skeletal muscle)	SLDH	?	0.07	—	—	—	$[(SLDH)Zn_?](NAD)_?$
Alkaline phosphatase (porcine kidney)	—	?	0.15	—	—	—	—
Alkaline phosphatase (*Escherichia coli*)	—	80,000	0.17	2.1	—	—	—

* NAD, previously known as DPN.

C. Synthetics
   None

D. Natural Inorganic Sources
   1. Calamite (zinc spar)
   2. Sphalerite (zinc blende)
   3. Zincite
   4. Willemite
   5. Franklinite
   6. Zinc spinel (gahnite)

The element makes up 0.004% of the earth's crust and is twenty-fifth in order of abundance.

The normal abundance of zinc in soil is 80 ppm ranging from 10-300 ppm (25).

Biological Data

I. Acute Toxicity

Substance	Animal	No.	Route	Dosage (mg/kg)	Determin.	Ref.
$ZnCl_2$	Mouse		i.p.	20	MTD	198
$ZnCl_2$	Mouse		i.p.	31	LD_{50}	198
$ZnCl_2$	Mouse		i.p.	48	LD_{100}	198
$ZnSO_4$	Mouse		p.o.	405	MTD	92
$ZnSO_4$	Mouse		p.o.	611	LD_{50}	92
$ZnSO_4$	Mouse		p.o.	891	LD_{100}	92
Zn^{++}	Mouse		i.p.	9.6	MTD	198
Zn^{++}	Mouse		i.p.	14.9	LD_{50}	198
Zn^{++}	Mouse		i.p.	23.0	LD_{100}	198
$ZnSO_4$	Rat		p.o.	810	MTD	92
$ZnSO_4$	Rat		p.o.	1374	LD_{50}	92
$ZnSO_4$	Rat		p.o.	2430	LD_{100}	92
$ZnSO_4 \cdot 7H_2O$	Rat	2	p.o.	500	MTD	237
$ZnSO_4 \cdot 7H_2O$	Rat	4	p.o.	750	LD_{50}	237
$ZnSO_4 \cdot 7H_2O$	Rat	4	p.o.	1000	LD_{100}	237
$Zn(OAc)_2 \cdot 7H_2O$	Rat	2	p.o.	500	MTD	237
$Zn(OAc)_2 \cdot 7H_2O$	Rat	4	p.o.	750	LD_{50}	237
$Zn(OAc)_2 \cdot 7H_2O$	Rat	4	p.o.	1000	LD_{100}	237
$Zn(OAc)_2 \cdot 7H_2O$	Rat		p.o.	1600-3780 (2460)	LD_{50}	538
$ZnCl_2$	Rat	15	p.o.	500	MTD	237
$ZnCl_2$	Rat	48	p.o.	750	LD_{50}	237
$ZnCl_2$	Rat	13	p.o.	1000	LD_{100}	237
$ZnCl_2$	Rabbit	4	p.o.	500	MTD	237
$ZnCl_2$	Rabbit	6	p.o.	750	LD_{50}	237
$ZnCl_2$	Rabbit	2	p.o.	1000	LD_{100}	237

Cowan reported that an Indian woman took approximately 28000 mg of zinc sulfate by mistake. She was admitted to a hospital, at which time she was acutely collapsed and restless. On the second day, she complained of abdomina pain of a colicky nature. There was a persistent tachycardia of 90-100/minute. A urinalysis showed no abnormalities. On the fifth day, she collapsed and became semi-comatose with a marked ketosis; blood sugar was 380 mg%, and her urine was laden with sugar, ketones, and albumin. She died on the fifth day. A necropsy was performed on the sixth day. Death was attributed to renal failure caused by zinc sulfate intoxication. Hemorrhagic pancreatitis and hyperglycemic coma resulted from the zinc sulfate (120).

Laurence reported that he and his wife suffered from pains in the legs and back, headache, general malaise, and nasal coryza after moving to a bungalow in which the water supply came though a galvanized pipe from the water main. After several months, he had the water analyzed, and it was found to contain 40 ppm zinc. After replacing the galvanized pipe with polyethylene, the symptoms of both, gradually disappeared over a period of several months. Laurence attributed his symptamology to acute zinc intoxication (331).

It seems unlikely that zinc at this level resulted in the aforementioned syndrome. Most probably the galvanized pipe contained other toxic metal ions, Cd^{++} or Pb^{++} for example. Nevertheless, it was a fact that some factor in the water was responsible for the toxicosis and it had been establizhed that Zn^{++} was present.

ZINC GLUCONATE

Biological Data

I. Acute Toxicity

See Zinc Salts

II. Short-Term Studies

No information available.

III. Long-Term Studies

No information available.

IV. Special Studies

No information available.

ZINC CHLORIDE

Biological Data

I. Acute Toxicity

See Zinc Salts

II. Short-Term Studies

Rats

Gross, et al., fed a special sub-optimal diet to individually housed female albino rats 21-24 days-old by syringe per os 6 days a week for 9 weeks. This diet resulted in a normal appearance of the animals, but the nutritive value thereof was insufficient to enable rats to maintain the growth associated with a standard laboratory diet (224).

Eight rats were fed this sub-optimal diet and 4 hours later were fed 4 mg of zinc chloride (an initial dosage of 100 mg/kg) for 6 days a week. Within 3-5 weeks, these rats showed retardation of growth and various skin manifestations commonly associated with pantothenic acid deficiency. During the sixth week, these animals were fed 150 micrograms of calcium pantothenate daily. Within 3 weeks, their appearance returned to normal (224).

Further nutrition experiments were conducted in which Gross, et al., found that zinc chloride fed at levels of 75-250 mg/kg/day for 2 weeks resulted in toxic effects attributable to mechanisms of toxicity other than pantothenic acid deficiency (224).

One hundred Wistar rats housed in wire cages were divided into 4 groups of 25 each. Each of these groups was further split so that 8, 8, and 9 rats were housed as a group. At the start of the experiment, the 4 groups of rats were provided zinc chloride as a liquid source in 0, 0.5, 1.0, and 5.0% aqueous solution. Rats would not drink these solutions, and food had to be dampened with the solutions in order to dose the rats. The groups at each dosage level of zinc chloride received 0, 60, 120, or 600 mg/day respectively. The first 3 regimens were continued for 15 months, the fourth for 6 months (626).

The amount of food eaten and the amounts of solutions used daily were recorded. Rats were weighed every other day. Those animals dying were carefully examined, and specimens of tissue (intestinal, renal, lung, spleen, heart, hepatic, and adrenal) were subjected to pathological examination (626).

There were no apparent effects in the first 3 groups; these groups included those fed 0, 300, and 600 mg/kg/day for 15 months. However, in the fourth group fed zinc chloride at a level of 3000 mg/kg/day, there was an abrupt weight loss within 2 weeks. Death took place about 2 weeks after commencement of the dosage, 13 rats died within the following 10 days. Six rats survived for 6 months and seemed to have developed at least some tolerance to the zinc chloride. Zinc chloride at this level exerted a corrosive action on the gastrointestinal tract and resulted in renal damage (626).

III. Long-Term Studies

Rats

Heller and Burke chose vigorous young rats and placed them in cages so that each lot would be comparable as far as possible. One cage of these rats was fed a basal diet, one cage was fed zinc as zinc chloride at a level of 0.25% in the diet, and a third cage was fed zinc as zinc chloride at a level of 0.5% in the diet (248).

The rats were mated, and their offspring were put on the same zinc regimen as their parents. This was continued for 3 generations. After full growth of the test animals had been reached, they were sacrificed and autopsied. Heart, lungs, liver, spleen, kidneys, and gonads were examined, weighed, and compared to those of controls (248).

TABLE I

Zn as $ZnCl_2$	M	F	No. of Litters	Young	Surviving Young	Dead Young
0%	3	1	2	18	16	2
0.25%	2	2	4	25	20	5
0.5%	2	7	7	46	27	19

Growth of rats was normal, and no toxic effects were reported. Mating took place at the normal age, and offspring appeared to be normal; although, there was an increased incidence of stillbirth at the 0.5% level of zinc as zinc chloride. Autopsies performed on adult animals showed no abnormalities (248).

IV. Special Studies

Carcinogenic

On the basis of preliminary work done over a ten year period, Halme designed several experiments to test the possible carcinogenic effect of zinc. These experiments were executed using 2 strains of tumor-resistant and 2 strains of tumor-sensitive (C_3H and A/Sn) mice and were continued over several generations. Zinc was dosed as the chloride from 0-200 mg/l in the drinking water. Halme found that zinc at a level of 10-20 mg/l resulted in a highly significant increase of carcinomas in test subjects. The tumor frequency of the succeeding generations progressively increased while the tumor induction time decreased, indicating that the effect of Zn is accumulated in the following generations. Halme pointed out that zinc is often found in the drinking water of man at levels of 5 mg Zn/l and sometimes higher than 50 mg Zn/l. He noted that the tumor induction time of the mice corresponds to the cancer age of man (239).

De Szilvay performed a series of experiments on mice to examine the carcinogenic effect of zinc. Mineral water with a zinc content of 0.016 mg/l was used as drinking water (137).

In the first experiment, 10-20 mg of zinc chloride per liter was added to the drinking water of tumor-resistant mice. Of the 100 test mice, 10 developed cancer (seminoma, cancer of the bone marrow, and cancer of the uterus), the first tumor appearing 6-8 months after the start of the

experiment. Of the 40 control mice, receiving only the mineral water, none developed cancer (137).

Seventy-five mice descended from tumor-susceptible mice were maintained on drinking water containing 10-20 mg Zn/l. Of these, 9 developed cancer (pulmonary adenoma, cancer of the marrow, uterine cancer, and hemangioma), the first tumor appearing in 5 months. One case of pulmonary adenoma and one of hemangioma were found in the 25 control mice (137).

Finally, 100 mice were organized into groups of 20 and subjected to levels of 0-100 mg of zinc chloride/l in their drinking water. The experiment continued for 3 years, always including the mice born during the experiment, but keeping them under special treatment and observation. Of the 100 original mice, 16 died from carcinoma of the uterus, seminoma, cancer of the mammaries, and pulmonary cancer. One hundred mice, covering 4 generations, were selected from those born during the experiment and maintained, from birth, on the various levels of zinc chloride. From these, 30 deaths were observed due to cancer in the following forms: sarcoma, leiomyoma, pulmonary adenoma, tumor of the granular cells, and fibrosarcoma. The frequency of tumors in subsequent generations was found to progressively increase and the time required for the formation of tumors became increasingly shorter. The most effective concentration of zinc was 5.0-20.0 mg Zn/l (137).

ZINC OXIDE

Biological Data

I. Acute Toxicity

See Zinc Salts

II. Short-Term Studies

Chickens

Five hundred White Leghorn male chicks, grown to 1 week of age on the basal diet, were allotted on the basis of weight into 5 replicates of 10 chicks each for each of the 10 levels (see table). Graded levels of zinc were added to the basal diet at the expense of corn. The chicks were raised in heated batteries and were supplied feed and water ad lib (476).

Food consumption and individual weights were determined at the end of the 5th week. Mortalities were recorded. Following is a tabulation of the experiment (476):

TABLE 1

Group	Zn as ZnO (ppm)	Survivors (of 50)	Avg. Wt. (g)	Feed/Gain
1	0	50	485	2.86
2	200	50	492	2.86
3	300	50	496	2.86
4	400	49	476	2.94
5	500	50	494	2.78
6	600	50	488	2.86
7	700	50	471	2.86
8	800	50	474	2.94
9	900	50	478	2.86
10	1000	50	473	2.94

In another series of feeding studies, Roberson and Schaible allotted 1-day-old White Rock male chicks on the basis of weight into 3 replicates of 10 chicks for each level of zinc dosage. Feed and water were supplied ad lib, and the study was continued for 4 weeks. Following is a tabulation (476):

TABLE 2

Zn as ZnO (ppm)	Avg. Wt. (g)	Survivors (of 30)	Feed/Gain
0	476	29	1.85
1000	488	29	1.72
2000	441	30	1.89
3000	337	29	2.27

In a third series, Roberson and Schaible allotted 1-day-old White Rock male chicks again; this time the zinc dosage levels were 0, 1000, and 1500 ppm. The chicks were reared in the same fashion as in the two preceeding studies. Following is a tabulation of the results (476):

TABLE 3

Zn as ZnO (ppm)	Avg. Wt. (g)	Survivors (of 40)	Feed/Gain
0	491	38	1.61
1000	497	38	1.67
1500	455	38	1.85

At levels of 1000 ppm, zinc as zinc oxide did not depress chick growth; however, at 2000 and 3000 ppm, growth was depressed. The 1500 ppm level seemed to be the lowest at which growth was depressed by zinc (476).

Johnson, et al., conducted feeding experiments with cross-bred broiler chicks which were assigned to lots of 20 (10 male, 10 female). For the first 4 weeks, these chicks were housed in starting batteries and later transferred to other batteries. The first experiment lasted 10 weeks, the second 10-16 weeks (288).

In experiment 1, there were 8 lots of 20 chicks; in experiment 2, there were 12 lots of 20 chicks. Zinc as the oxide, was mixed in the diet at various levels, and food and water were provided ad lib. Following are the results of these experiments (288):

TABLE 4

	Average Live Weight (g)				Feed Efficiency	
Zinc Level (ppm)	10 wks	12 wks	14 wks	16 wks	0-10 wks	10-16 wks
Experiment 1						
Control (45)	1680	2058	2433	2705	.390	.201
540	1680	2077	2416	2723	.368	.186
732	1690	1998	2383	2626	.386	.172
988	1620	2035	2337	2543	.360	.181
1329	1682	2039	2419	2706	.392	.198
1784	1602	2044	2346	2641	.389	.197
2391	1522	1889	2295	2579	.378	.204
3200	1432	1904	2221	2459	.372	.205
Experiment 2						
57	1776	2179	2632	2933	.388	.214
979	1806	2206	2629	2913	.388	.194
1974	1715	2020	2482	2826	.384	.208
2918	1596	1988	2330	2707	.389	.210
3875	1252	1687	2132	2501	.366	.231
4941	1164	1479	1892	2192	.360	.225

In experiment 2, when the chicks were 10 weeks-old, 2 males and 2 females were randomly selected, sacrificed, and their spleens and livers determined for zinc. Zinc regimens were discontinued at 10 weeks in experiment 1 and in 10-16 weeks in experiment 2. At 16 weeks, liver and spleen determinations for zinc were again carried out in experiment 2 (288).

The results of the experiments indicated that chickens tolerate at least 1000 ppm of zinc added to the diet. In the first experiment, growth was not markedly depressed on diets containing less than 2391 ppm. In the second experiment, there was a slight growth depression evident at a level of 1974 ppm zinc and significant growth depression at 2918, 3875, and 4941 ppm. Liver zinc determinations revealed that zinc was stored in the liver when excess zinc oxide was fed, but an appreciable portion of this zinc was lost upon discontinuation of the zinc dosage (288).

Tahara, et al., divided 45 Rock Horn male chicks 5-days-old into 3 groups of 15 each. One group was fed a basal diet; the other 2 groups were fed the basal diet with a component of zinc as the oxide at 2000 or 3000 ppm. The chicks were housed in plastic-coated batteries and were provided food and water ad lib throughout the 26 day experimental period. Following are the results (572):

TABLE 5

Group Zn as ZnO	Increase Body Weight (g)	Comp. Cont.	Food Intake (g)	Comp. Cont.	Water Intake (ml)	Comp. Cont.
Control	236	100	9268	100	14892	100
(2000 ppm)	250	106	9000	97	14275	96
(3000 ppm)	226	96	8392	91	13997	94

Zinc at the highest level exhibited little toxicity for chicks. At 3000 ppm, the food intake seemed to be slightly depressed; otherwise, there was little significant difference among control and test groups (572).

Using 200 one-day-old New Hampshire chicks, Mehring, et al., found that levels of zinc in the diet up to 823 ppm for a period of 9 weeks resulted in no effects on growth rate, weight, or feed efficiency (374).

Rats

Drinker, et al., performed several feeding studies concerned with the effects of zinc (as zinc oxide) on rats. Test rats were divided into 2 groups. Group 1 rats were housed individually and were put on a zinc regimen at the age of 12 weeks. Group 2 rats were housed collectively according to dosage and were put on a zinc regimen at the age of 22 weeks. During the course of the experiment, the rats were weighed weekly or biweekly. At the conclusion of the experiment, each animal was autopsied, and gross and microscopic studies and zinc analyses were made on blood, skin, muscle, liver, lung, kidney, brain, gonad, adrenal, spleen, and pancreas tissue. The following table shows the regimens (143):

Husain reported that 104 patients tested (52 test, 52 control) for healing time of leg ulcers were given either 660 mg/day lactose or 660 mg/day zinc sulfate. Ulcers of the group fed zinc sulfate healed within 32 days on the average; the lactose group healed within 77 days on the average. Mild diarrhea in 3 patients was interpreted by Husain to be the only noted toxic effect attributable to the zinc sulfate (275).

Dr. Cohen treated elderly patients with bedsores by giving them 440-660 mg of zinc sulfate daily. The patients either became ambulant or remained so. No ill-effects were observed in patients receiving zinc sulfate for 106 days (114).

Carruthers reported that elderly patients treated for chronic leg ulcers at a dosage of 660 mg/day of zinc sulfate have not shown any untoward effects from the dosage. Furthermore, none complained of nausea, even after direct questioning (87).

III. Long-Term Studies

Rats

Four groups of 8 Osborne Mendel weanling rats (4 males, 4 females) were fed ad lib a basal diet containing 0, 100, 500 and 1000 ppm of zinc as the sulfate (7 hydrate). The animals were housed individually, and food con-sumption and weight were recorded weekly. Eight complete blood counts, confined to the first 3 and last 5 months of the experiment, were made. Bone marrow smears were made at the termination of the study, 21 months after initiation. The animals were sacrificed and autopsied at the completion of the experiment (236).

Inspection of smears showed the occurrence of microcytosis, coupled with polychromasia in some cases and hyperchromasia in others. The blood changes occurred at all levels of feeding and were first observed at the 1000 ppm level on the resumption of blood studies at the 16th month. One month later, this change was noted at the 100 and 500 ppm levels (236).

There were no gross pathological changes attributable to zinc at these levels, but kidneys of male rats on 500 and 1000 ppm levels were larger and more granular than those on 0 and 100 ppm levels. The intake of zinc as the sulfate at the lowest level was 4-6 mg/kg/day for 77 weeks. At this level, pathogenic blood changes occurred (236).

Heller and Burke chose vigorous young rats and placed them in cages so that each lot would be comparable as far as possible. One cage of these animals was fed a basal diet, and a second cage was fed zinc as zinc sulfate at a dietary level of 0.25% (248).

The rats were mated and underwent the same regimen for 3 generations. After full growth of the test animals had been reached, an autopsy was con-ducted upon sacrifice of the rats. Heart, lungs, liver, spleen, kidneys, and gonads were examined, weighed, and compared to those of the controls (248).

Growth of rats was normal, and no toxic effects were observed. Mating took place at the normal age, and offspring appeared to be completely normal. Autopsies showed no abnormalities in test rats (248).

IV. Special Studies

Fetal Effects

Four yearling ewes were fed zinc sulfate. Two ewes were fed zinc sulfate at a level of 5 mg/kg/day for the first 45 days of gestation; the other two ewes were fed zinc sulfate at the same dosage throughout the gestation period (147 and 152 days). All ewes and lambs were sacrificed at parturition. Blood samples were collected, and the following blood analyses were made weekly throughout the experimental period: packed cell volume, hemoglobin, plasma urea-N, serum glucose, and serum protein. A BSP was performed weekly. There were no observed toxic effects of zinc; however, zinc concentrations were higher in the livers and possibly the bones of the test fetal lambs than in controls (283).

Carcinogenic

Groups of pregnant mice, and the litters subsequently born to them, were exposed to zinc sulfate in the drinking water at levels of 5000 or 1000 ppm zinc or to distilled water. At the time of this report, animals had been on the zinc regimen for over a year without any evidence of carcinogenesis attributable to zinc (60).

TABLE 4

Group 1	Avg. Daily Dose (mg Zn)	Time (weeks)	Hemoglobin	RBC	WBC
1	0.5	42	85	9673000	21200
2	2.7	42	100+	8032000	11800
3	5.4	42	90	9862000	7600
4	7.0	43	90	9537000	7200
5	10.4	39	90	10071000	9100
16	13.7	37	90	12013000	11400
7	17.9	36	90	11797000	11300
8	22.8	38	90	11464000	8500
Control 1	0	34	95	11536000	16000
Control 2	0	34	95	10116000	17100
Group 2					
1	34.4	35	85	12269000	10800
2	34.4	36	--	--------	-----
3	34.4	35	85	10921000	7000
Control 1	0	34	80	10626000	6300
Control 2	0	34	80	10824000	15500
Control 3	0	34	95	12852000	11800
Control 4	0	34	90	11967000	9300
Control 5	0	35	90	11356000	9900

Daily doses of 0.5-34.4 mg of zinc (calculated from zinc oxide) administered orally to rats in drinking water for 35-53 weeks showed no evidence of toxicity (143).

Sadasivan reported that 3 groups of 4 rats each were fed a stock diet. One group was fed zinc oxide as a 0.5% component, a second group was fed zinc oxide as a 1.0% component, and a third group was maintained as control. The purpose of the 15-day-long test was to ascertain the effect of zinc levels on the metabolism of nitrogen, phosphorus, and sulfur (498).

See biochemical section for test results.

Cats

Ten cats, housed individually, were fed canned salmon and milk once a day. Zinc as the oxide was mixed as a dry powder in the food and administered daily. The dosages varied from 175-1000 mg. The following table is a summary of the dosage regimen (142):

TABLE 5

Cat	Sex	Dosage (Zn mg/kg/day)	Duration (weeks)
1	Male	33.8	10
2	Male	41.1	10
3	Female	44.0	31
4	Female	52.7	31
5	Female	64.4	11
6	Male	66.2	11
7	Female	121.4	53
8	Female	265.4	16
9	Male	340.4	21
10	Male	420.2	21

The cats were weighed weekly and observed daily for vomiting, diarrhea, or other signs of illness. Urine specimens were examined for albumin, sugar, and the sediment for casts, pus cells, blood cells, etc. Hemoglobin determinations and blood cell counts were made on each animal before autopsy. At the termination of the experiment, the cats were sacrificed and autopsied (142).

There were no toxic effects of zinc evident in 7 of the cats, but in 3 of the cats there were fibrous changes in the pancreas (142). Failure of the workers to include control animals makes it difficult to interpret these pancreatic changes.

Dogs

Drinker, et al., fed 3 dogs zinc as the oxide in the diet from 3-15 weeks. The following table shows the dosage regimen (142):

TABLE 6

Dog	Sex	Dosage (Zn mg/kg/day)	Duration (weeks)
1	Male	36.1	19
2	Female	59.9	3
3	Female	76.5	15

The dogs were weighed weekly and observed daily for signs of illness, vomiting and diarrhea; urine specimens were examined for albumin, sugar, and the sediment for casts, pus cells, blood cells, etc. Hemoglobin determinations were made on each dog before they were sacrificed and autopsied at the termination of the study. There were no toxic effects of zinc evident at these levels of challenge in test dogs (142).

Sheep

Ott, et al., conducted experiments in order to determine maximum amounts of zinc that could be fed to sheep without causing detrimental effects. In experiment 1, 30 wether lambs were divided into 5 groups of 6 each. These

lambs were fed a basal diet for 2 weeks and a zinc regimen for 10 weeks at levels of 0, 500, 1000, 2000, or 4000 ppm in the diet. Experiment 2 was similar except that 80 sheep were allotted to 8 groups of 10 each and fed zinc as a 0, 500, 1000, 1500, 2000, 2500, 3000, or 3500 ppm dietary component (432).

The first indication of zinc toxicity in experiment 1 was a reduction in food consumption within 6-10 weeks at zinc levels of 2000 and 4000 ppm. Sheep at 500 and 1000 ppm consumed more food and gained faster, exhibiting greater food efficiency, than did controls (432).

In the second experiment, sheep fed zinc as the oxide at 1500 ppm showed depressed food intake, growth rate, and food efficiency. At higher levels, these effects were dramatic. Animals at 2000 ppm levels and higher had increased mortality (432).

Cattle

Ott, et al., divided 16 calves into 4 groups of 4 each and fed them as follows (434):

TABLE 7

Group	Zn as ZnO (ppm)	Daily Gain (lbs)	Food Consumption (lbs)	Food Cons/100 lbs Gain
1	0	2.69	19.95	741
2	1000	2.25	23.94	1064
3	2000	0.48	18.48	3804
4	3000	-0.13	15.10	0

At levels of 2000 ppm, zinc as the oxide depressed growth severely in calves. At 1000 ppm, the effect is questionable.

In another study, Ott, et al., divided 60 calves into 6 groups of 10 (5 male, 5 female) at each dosage level of zinc. The results of the 71 day feeding study follow:

TABLE 8

Group	Sex	Zn as ZnO (ppm)	Daily Gain (lbs)	Food Intake (lbs)	Food Intake/100 lbs Gain
1	M	100	2.11	21.70	1027
2	M	500	2.24	21.01	934
3	M	900	1.82	18.59	1020
4	M	1300	1.58	20.45	1298
5	M	1700	0.33	17.59	5400
6	M	2100	0.55	18.91	3410
7	F	100	1.77	17.95	1014
8	F	500	1.85	17.22	933
9	F	900	1.60	17.26	1076
10	F	1300	1.30	18.44	1422
11	F	1700	0.71	17.79	2499
12	F	2100	0.42	16.52	3964

At a level of 1700 ppm, zinc as the oxide exhibits severe growth depression for male and female calves over a 71 day period. There is some evidence that the 1300 ppm level may be near the toxic threshold for calves in a short-term regimen with zinc oxide.

III. Long-Term Studies

Heller and Burke chose vigorous young rats and placed them in cages so that each lot would be comparable as far as possible. One cage of these animals was fed a basal diet, and a second cage of these animals was fed a diet containing a 0.5% level of zinc as the oxide (248).

The rats were mated and underwent the same zinc regimen for 3 generations. After full growth of the test animals had been reached, an autopsy was conducted upon sacrifice of the rats. Heart, lungs, liver, spleen, kidneys, and gonads were examined, weighed, and compared to those of the controls (248).

Growth of rats was normal, and no toxic effects were observed. Mating took place at the normal age, and offspring appeared to be completely normal. Autopsies showed no abnormalities in test rats (248).

IV. Special Studies

Reproduction and Fetal Effects

Nulliparous female CPE strain Sprague-Dawley rats ranging in weight from 195-245 g were housed individually and fed a basal diet or a basal diet + 0.4% zinc as zinc oxide ad lib. Water was provided ad lib. Then experiments were run.

In experiment 1, 10 rats were mated and then randomly assigned to the basal or .4% zinc diet. At fetal age 16 days, all rats were killed. In experiment 2, the same regimen was followed except that the rats were killed at fetal age 21 days. In experiment 3, the same regimen was followed as in the other 2 experiments except that 12 rats were used, and these rats were killed at fetal age 22 days (123).

At the appropriate fetal age, mothers were stunned by a blow on the head, decapitated, and exsanguinated. Fetuses were removed via abdominal incision and were stunned, decapitated, and exsanguinated. Tissues were removed, weighed, and homogenized. Homogenates were analyzed for succinic dehydrogenase, cytochrome oxidase, and xanthine oxidase. Sera of mothers were analyzed for ceruloplasmin, and blood hemoglobin was measured. Adrenals, kidneys, spleen, thymus, gastrocnemius muscle, and brain were removed from mothers at day 22, dried to constant weight, and determined for several metals (123).

No change was found in dry weights of the liver and heart of 16, 21, and 22-day-old fetuses from mothers fed excess zinc. Dry weight of body was significantly less in the 22-day-old fetuses from these mothers. In

addition, at day 22, hemoglobin was significantly lower in the maternal rat fed 0.4% zinc (123).

Thompson, et al., fed 3 pairs of rats diets containing zinc oxide suspensions at average daily levels for the pairs of 6.5-38 mg of zinc during gestation and lactation. Prior to mating, the females and the males had received daily doses of zinc salt solutions ranging from 9.7-34.4 mg of zinc in their diets for 29 weeks. No effects were noted upon the health of the parents, their fertility, or the health of their offspring (580).

ZINC STEARATE

Biological Data

I. Acute Toxicity

See Zinc Salts

II. Short-Term Studies

No information available.

III. Long-Term Studies

No information available.

IV. Special Studies

Irritant Effect Study

Harding injected an aqueous suspension of zinc stearate through the larynx into the lungs of rats and into the peritoneal cavity of guinea pigs. Approximately 100 mg of zinc stearate resulted in death of the rats within 10 minutes. One-third of the guinea pigs receiving the same dosage i.p. died; the remainder survived until the 35th day, at which time they were sacrificed and examined (245).

Further experimentation with 50 mg resulted in similar consequences. Harding concluded that zinc stearate in aqueous suspensions is an acute irritant in rats when inspired and in guinea pigs when injected i.p. (245).

Biological Data

I. Acute Toxicity

See Zinc Salts

II. Short-Term Studies

Chickens

One-day-old White Rock male chicks were allotted on the basis of weight into 3 replicates of 10 chicks for each level of zinc as the sulfate. Feed and water were supplied ad lib throughout the 4 week duration of the experiment. Following is a tabulation (476):

TABLE 1

Group	Zn as $ZnSO_4$ (ppm)	Average Weight (g)	Survivors (of 30)	Feed/Gain
1	0	476	29	1.85
2	1000	464	30	1.69
3	2000	419	28	1.92
4	3000	282	29	2.44

In another series of experiments, Roberson and Schaible allotted White Rock male chicks into groups at 0, 50, 1000, and 1500 ppm levels of zinc as the sulfate and reared these chicks as in the preceding study. The results are as follows (476):

TABLE 2

Group	Zn as $ZnSO_4$ (ppm)	Average Weight (g)	Survivors (of 40)	Feed/Gain
1	0	491	38	1.61
2	50	500	40	1.75
3	1000	470	39	1.69
4	1500	402	39	1.96

Levels above 1000 ppm Zn depressed growth of chicks over a 4 week period. There is some indication that the 1000 ppm level of zinc as the sulfate may depress growth slightly (476).

A total of 45 Rock Horn male chicks 5 days-old were divided into 3 groups of 15 each. One group was fed a basal diet; the other 2 were fed this same diet with a 2000 or 3000 ppm component of zinc as zinc sulfate. Chicks were housed in plastic-coated batteries and were provided food and water ad lib throughout the 26 day experimental period. Following are the results (572):

Table 3

Zn as ZnSO4 (ppm)	Increase Body Wt (g)	Comp % Con.	Food Intake (g)	Comp % Con.	H2O Intake (ml)	Comp % Con.
0	236	100	9268	100	14982	100
2000	203	86	7783	84	13823	92
3000	153	65	7358	80	11293	76

Mortality rate of chicks was much higher at 3000 ppm zinc than at lower levels. The 2000 and 3000 ppm levels of zinc resulted in a growth depression, shortening and thickening of the tibia, poor feathering, and anemia in chicks (572).

Rats

Male albino Wistar rats housed individually were separated into a control group of 16 rats and a test group of 15 rats. Both groups were fed a stock diet for 10 days. The drinking water of the test group contained zinc as the sulfate at a level of 20-40 mg/kg/day (298).

The animals were wounded and sutured, to observe the effect of zinc sulfate on wound healing. Animals were sacrificed on the tenth day (298).

There was no evidence of systemic toxicity in animals receiving per os zinc sulfate at a level of 20-40 mg/kg/day for 10 days (298).

Weanling Wistar rats were allotted into 2 groups and fed a basal ration or a basal ration with a 1000 ppm zinc component as zinc sulfate. Rats were maintained on this regimen for 14 weeks. Liver-Zn, kidney-Zn, and femur-Zn were determined as well as Cu and Mo levels of other tissues. Results are as follows (323):

Table 4

Zn as ZnSO4 (ppm)	Wt Gain (g/8 wks)	Liver-Zn (ppm)	Kidney-Zn (ppm)	Femur-Zn (ppm)
0	115	65	97	149
1000	105	100	96	177

From the above results, it is apparent that zinc fed to rats at the 1000 ppm dietary level results in an increase of zinc in the liver, possibly in the femur; however, no toxic effects were attributed to zinc over the 14 week period of this experiment. Growth rate was not significantly affected (323).

Dogs

A litter of 6 Dalmation puppies 10-weeks-old was selected for a feeding study. Four of the pups were given zinc sulfate (7 hydrate) at a daily level of 200 mg/kg/day at the beginning of the feeding study by means of a gelatin capsule. Complete blood counts were taken every 2 weeks at the start of the study and at longer intervals thereafter (236).

After 7 weeks of zinc sulfate administration most of the dogs began to vomit considerably after their doses, the level, therefore, was reduced to 100 mg/kg/day. After 3 weeks, one of the dogs began to vomit, its dosage was reduced to 50 mg/kg/day; the other 3 dogs held at the 100 mg/kg/day level for 32 weeks, then they too began to vomit. At this time their dosages were likewise reduced to 50 mg/kg/day (236).

All dogs showed a change attributable to zinc sulfate in that the bone marrow was uniformly slightly hyperplastic as compared to that of control animals (236).

Swine

Ten-week-old Hampshire pigs were allotted into 2 groups and fed a basal diet or a basal diet containing 1000 ppm zinc component as the sulfate. These swine were fed for 27 weeks. Weight and food efficiency were recorded. Histological studies were performed on sections taken from the cerebrum, cerebellum, cervical cord, thoracic cord, and lumbar cord. Similar studies were also performed on leg joints and gluteal musculature (323).

At the 1000 ppm level, zinc as the sulfate showed no effects on growth or food conversion. Histological studies revealed no obvious pathology in swine fed 1000 ppm zinc sulfate for 7 months (323).

Milosavljevic, et al., in contrast had very different results. They conducted 2 feeding studies in which the effects of dietary zinc sulfate were examined in dry and wet diets. In the first study, 3 groups of 8 English great white pigs 2½ months-old were fed 0, 100, or 200 ppm zinc sulfate in a dry diet. This diet was provided ad lib for 3½ months (390).

In the second study, an identical regimen was executed except that a wet diet was fed twice daily for 3½ months. In both studies, weight, food consumption, and conversion ratios were determined weekly (390).

Essentially, the experiments indicated that zinc sulfate at the 2000 ppm level resulted in decreased food intake and depressed growth (390).

Man

Brewer, et al., gave 14 patients suffering from decubitus ulcers either 660 mg/day of zinc sulfate or a lactose placebo. Seven patients received zinc, 7 the placebo (63).

Prior to treatment, serum and urine zinc determinations were made and repeated monthly throughout the testing period of 4 months. Urinalyses, blood counts, and blood chemistries were also run before, during and after the study (63).

There were no significant changes in white blood counts, hemoglobin, hematocrit, total proteins, albumins, BUN, or creatinine either during or after the zinc sulfate regimen. There was no evidence of toxicity of zinc sulfate for man at a dosage of 660 mg/day for 4 months (63).

ZINC ACETATE

Biological Data

I. Acute Toxicity

See Zinc Salts

II. Short-Term Studies

Chicks

Klussendorf and Pensack reported that zinc as zinc acetate added to the diet of chicks for an unspecified length of time resulted in a slight growth depression at the 2000 ppm level. No effect was noted at a dosage level of 1000 ppm in the diet (306).

Rats

Gesswein administered zinc acetate in drinking water to 2 groups of 25 rats: 1 group, a BDIII tumor-sensitive, and the other a non-sensitive strain. Ten control animals received tap water. All animals were housed individually and received the same stock diet (206).

The rats were 6-months-old at the initiation of the 75 mg/rat/day zinc acetate regimen. This level was raised to 600 mg/rat/day - a severely toxic level. The dosage was lowered to 400 then to 300 mg/rat/day. At this level, test animals were able to endure zinc acetate. The rats were weighed every 7-10 days for 52 weeks at which time they were sacrificed and histologic studies conducted on the gastrointestinal tract, genitourinary tract, pancreas, adrenals, and brain (206).

Within 7-10 weeks, test subjects developed scraggly coats. By the 18th week, a zinc tremor appeared; this tremor disappeared by the 22nd week. There seemed to be no specific viscerol changes attributable to zinc; however, a peculiar feature occurred when it was realized that the zinc-dosed rats were highly resistant to a respiratory infection that decinated control animals (206).

Salant reported that rats receiving 50-105 mg/kg/day of zinc acetate for 4 months kept their weight (that is, no loss) but seemed to exhibit a disturbance of renal function (500).

III. Long-Term Studies

No information available.

ZINC CARBONATE

Biological Data

I. Acute Toxicity

See Zinc Salts

II. Short-Term Studies

Chickens

One-day-old White Rock male chicks were allotted on the basis of weight into 3 replicates of 10 chicks for each level of zinc carbonate. Food and water was supplied ad lib throughout the 4 week duration of the study. Following are the results (476):

TABLE 1

Group	Zn as Zinc Carbonate (ppm)	Average Weight (g)	Survivors (of 30)	Feed/Gain
1	0	476	29	1.85
2	1000	483	30	1.72
3	2000	407	29	2.08
4	3000	214	23	3.45

In another series of experiments, Roberson and Schaible allotted White Rock male chicks into groups at 0, 1000, and 1500 ppm of zinc as zinc carbonate in the diet and reared these as in the preceding experiment. These results follow (476):

TABLE 2

Group	Zn as Zinc Carbonate (ppm)	Average Weight (g)	Survivors (of 40)	Feed/Gain
1	0	491	38	1.61
2	1000	490	40	1.79
3	1500	390	40	2.00

Levels of 1000 ppm zinc did not influence growth, food efficiency, or survivability; however, levels of 1500 ppm depressed growth. At 3000 ppm, zinc carbonate resulted in a 30% mortality of chicks within 4 weeks (476).

Klussendorf and Pensack added zinc (as zinc carbonate) at the level of 1000 or 2000 ppm to the ration of an unstated number of chickens for 71 days. The 2000 ppm level resulted in a slight growth depression (306).

A total of 45 Rock Horn male chicks 5-days old were divided by Tahara, et al., into 3 groups of 15 each. One group was fed a basal diet; the other 2 groups were fed a basal diet plus a component of zinc carbonate at either 2000 or 3000 ppm of the diet. The chicks were housed in plastic-coated batteries and were provided food and water ad lib throughout the 26 day testing period. Following are the results (572):

TABLE 3

Zn as Zinc Carbonate (ppm)	Increase Body Wt (g)	Comp. % Cont.	Food Intake (g)	Comp. %	Water Intake (ml)	Comp. %
0	236	100	9268	100	14892	100
2000	211	89	8488	92	13597	91
3000	175	74	7877	86	11887	80

Zinc as zinc carbonate at the 3000 ppm level resulted in an increased mortality rate and depressed growth. Observations on test chicks showed that poor feathering occurred at the 3000 ppm level. Blood and bone determinations indicated that zinc at the 3000 ppm dietary level resulted in a shortening and thickening of the tibia as well as anemia. Similar effects, though not so pronounced, resulted at the 2000 ppm level (572).

Rats

Smith and Larson fed 4-6 week-old Sprague-Dawley rats zinc as zinc carbonate at dietary levels of 0.4-1.0% for 4-6 weeks. The animals were housed individually and provided food and water ad lib. Hemoglobin determinations were made periodically, and at the end of the experiment, hemoglobin, RBC, WBC, red cell volume, and blood smears were determined (537).

At the 1% level, rats responded with a severe anemia in 3-5 weeks; mortality at this level was severe by the sixth week. At the 0.7% level, zinc resulted in a marked anemia for rats by the fourth week; however, mortality was not abnormal at this level (537).

Realizing that the 0.7% level of zinc was toxic but not lethal, Smith and Larson conducted 2 experiments concerning the effects of various trace elements (Fe, Cu, Co) on zinc toxicity. In the first experiment, they fed 80 30-40 day-old rats zinc at the 0.7% level and divided these animals into 16 groups of 5 each. Each group was supplemented with Fe, Cu, Co, or liver extract in different combinations in order to ascertain any effect other micronutrients might have on zinc toxicity. A second experiment on 40 rats was run to determine the effect of the liver extract. Complete blood work-ups (hemoglobin, hematocrit, RBC, WBC, etc) were done on the test animals in order to check the effects of these supplements on blood chemistry of zinc-fed animals (537).

Zinc at the 0.7% level induced a microcytic and hypochromic anemia in the test rats as well as subnormal growth. By feeding additional copper, Smith and Larson maintained higher hemoglobin levels in the rats; Fe, Cu, Co supplement maintained normal hemoglobin levels at the 0.7% zinc dosage. However, no supplement had any effect on growth depression resulting from an excess level of zinc (537).

Pigs

Brink, et al., conducted a series of short-term feeding studies with zinc carbonate to weanling pigs. In experiment 1, 36 weanling pigs were placed in groups of 6 on the basis of breeding, weight, and general condition. These groups were allotted at random to the zinc treatments and self-fed ad lib as a group for 42 days (66).

In experiment 2, 40 weanling pigs were allotted to groups of 5 at each level. In addition, 3% dicalcium phosphate was added as a 1% dietary component. Feeding procedure was identical to experiment 1. In experiment 3, 16 weanling pigs were placed into 2 groups of 8 each. One group was control; the other group was fed zinc as zinc carbonate at a 0.40% level (66).

Food consumption was recorded daily. Average daily gain and the gain/food ratio were determined. Careful post mortem examinations were carried out. Blood clotting time, prothrombin time, blood-Ca, blood-P, and liver-Zn were determined. Following are the results of experiment 1 (66):

TABLE 4

Zn as $ZnCO_3$ (%)	No.	Mortality	(Days) Duration	Avg. Daily Gain (lbs)	Gain/Feed	Avg. Hemoglobin (gm/100 ml)
0	6	0	42	1.56	0.36	12.99
0.05	6	0	42	1.62	0.35	12.50
0.10	6	0	42	1.56	0.34	12.39
0.20	6	2	36.3	1.24	0.31	10.87
0.40	6	3	33.2	0.77	0.23	13.54
0.80	6	1	29.5	0.26	0.18	12.55

The addition of 0.1% zinc was the maximum level tolerated. Higher levels produced depressed growth rates, food intakes, gain efficiencies - all symptoms of zinc toxicosis, arthritis, extensive hemorrhage in the axillary spaces, gastritis, catarrhal enteritis, congestion of the mesentery, and hemorrhages in the ventricles of the brain, lymph nodes, and spleen were observed. Feeding high levels of zinc frequently caused death within 21 days, but hemoglobin values appeared to be unaffected by the levels fed. Calcium as a 1% component had no effect on zinc toxicity (66).

III. Long-Term Studies

Rats

Heller and Burke chose vigorous young rats and placed them in cages so

that each lot would be comparable as far as possible. One cage of these rats was fed a basal diet, one cage was fed zinc (as zinc carbonate) at a level of 0.25% in the diet, and a third cage was fed zinc as zinc carbonate at this level with an addition of buttermilk (248).

The rats were mated, and their offspring were put on the same zinc regimen as their parents. This was continued for 3 generations. After full growth of the test animals had been reached, they were sacrificed and autopsied. Heart, lungs, liver spleen, kidneys, and gonads were examined, weighed, and compared to those of controls (248).

TABLE 5

Zn as Zinc Carbonate (%)	Males	Females	No. of Litters	Young	Surviving Young	Dead Young
0	3	1	2	18	16	2
0.25	2	2	7	53	50	3
0.25 + Buttermilk	2	2	4	31	30	1

Growth of rats was normal, and no toxic effects were reported. Mating took place at the normal age, and offspring appeared to be completely normal. Autopsies showed no abnormalities in test rats (248).

IV. Special Studies

Reproductive

Young rats were housed in groups of 5 (2 male, 3 female) and were supplied food and water ad lib. Zinc as zinc carbonate was incorporated in the basal diet at 0, 0.10, 0.50, or 1.00% levels. Observations were made on the effect of zinc on reproductive indices. Hemoglobin determinations were made throughout the 39 week study (568).

Growth of the rats was unaffected at the 0.50% level but was markedly depressed at the 1% level. Reproduction was, however, affected at the 0.50% level. After 5 months on this ration, females ceased to become pregnant (568).

Blood determinations showed that hemoglobin level of rats fed 0.10% zinc as the carbonate for 39 weeks was normal; however, rats fed at the 0.50% level were anemic by week 30. When the zinc carbonate regimen was discontinued, reproduction and hemoglobin level returned to normal (568).

Biochemical Aspects

I. Breakdown

No information available.

II. Absorption-Distribution

Van Campen and Mitchell studied the absorption of Zn^{65} in ligated segments of rat intestinal tract. They found that zinc is taken up most rapidly from the duodenum, somewhat more slowly from the ileum and the mid-section, and only slightly from the stomach (593).

In a review on zinc metabolism, Forbes stated that the absorption of zinc into the body occurs mainly through the walls of the small intestine. He noted that there is no evidence of active absorption or of an intestinal block to absorption, although a homeostatic feedback mechanism has been suggested for the regulation of zinc absorption and excretion (193).

By studying growth, survival, feed efficiency, bone development and the incidence of deficiency symptoms, Sullivan determined the availability of zinc in various compounds to Broad Breasted Bronze poults. He found that the zinc in zinc carbonate and $ZnSO_4 \cdot 7H_2O$ is readily available. The zinc in zinc chloride is perhaps slightly less available than the zinc in zinc carbonate and $ZnSO_4 \cdot 7H_2O$. Zinc oxide and $ZnSO_4 \cdot H_2O$ are relatively inferior sources of dietary zinc for poults (563).

O'Dell and Savage reported that chicks fed isolated soybean protein as a source of protein show a higher zinc requirement than those fed protein from casein. They found that phytic acid in the soybean oil meal is responsible for this effect (422).

The effect of phytic acid was reproduced in rats by McCall et al. (367) and confirmed in chicks in a later study by O'Dell et al. (423). Phytic acid is thought by some workers to reduce the effective concentration of zinc in the diet by 50% (196).

III. Metabolism and Excretion

In a review by Drinker et al. it is stated that zinc compounds taken into the gastrointestinal tract are converted in the stomach by the free hydrochloric acid or by free lactic acid, (if it is present), into zinc chloride and zinc lactate. Both compounds are then decomposed by the protein substances present, and protein compounds are formed which are either soluble or are in part dissolved by the free acids present. No information as to the further digestion of these compounds is given (142).

Drinker et al. studied the accumulation and excretion of zinc by feeding cats and dogs daily doses of zinc oxide ranging from 175 to 1000 mg for periods up to 53 weeks. They found that only a small fraction of absorbed ingested zinc leaves the body in the urine but that the main bulk of it is excreted into the alimentary tract - some of it directly, some by the liver into the bile, and possibly some by the pancreas - and ultimately leaves the body in the feces. The amount of zinc in the urine is markedly increased by feeding zinc oxide, though the total amount of zinc in the urine is still only a small fraction of that excreted. The authors noted that the animals were able to excrete abnormal amounts of zinc through the kidneys for months without any histological evidence of kidney damage. They found that the total zinc concentration of the zinc-fed animals increases slightly with moderate zinc dosing and somewhat more markedly with excessive zinc dosing, but falls practically to a normal level within a short time (two weeks) after zinc dosing is discontinued. The highest zinc concentrations were observed in those organs involved in the excretion of zinc (143).

In a later study by Drinker, et al. (142), the accumulation and excretion of zinc was found to be essentially the same in rats as that previously reported in cats and dogs (see preceeding paragraph).

After oral administration of zinc chloride to rats, Feaster et al. found that 67.6% of the dose was excreted in the feces during the first 24 hours, while 29.5% of the dose remained in the gastrointestinal tract and only 2.9% was absorbed. After 48 hours, 86.3% of the dose had been excreted in the feces, 5.8% remained in the gastrointestinal tract, and 7.9% had been absorbed. The total urinary excretion of the zinc chloride was found to be less than 0.2% of the dose. Tests for zinc chloride accumulation 96 hours after dosing showed that the kidneys, liver and pancreas contained the highest concentrations (181).

Richmond et al. studied the absorption and retention of orally administered ^{65}Zn in mice, rats, dogs, and man. They found that the data for biological retention can be accurately represented by multiple rate equations consisting of three exponential terms. They suggested that the individual components of the retention functions probably represent those gross rates of loss from a number of sites where zinc is bound by more than one mechanism rather than by loss from specific tissues or organs acting as separate components. The average effective biological half-life of ^{65}Zn in 4 human subjects was found to be 154 days. In rats, the bones and pelt account for essentially all of the ^{65}Zn making up the longest component of the retention function. Distribution studies in rats showed that peak tissue concentrations of ^{65}Zn are reached within 5 days after dosing (468).

IV. Effects on Enzymes and Other Biochemical Parameters

Sutton and Nelson reported that the blood sugar of rats may be increased 100-130% above the normal fasting level by administration of zinc chloride or zinc sulfate (30-65 mg Zn). They found that when the same amount of zinc is given with glucose, the blood sugar may be increased 150-190% above the normal fasting level in three hours (568).

The energy-linked accumulation of Mg^{++} by isolated heart mitochondria was found by Brierly et al. to be activated in vitro by the addition of Zn^{++}. They suggested that Zn^{++} may act directly on the process responsible for the uptake of Mg^{++}, perhaps by altering the permeability of the membrane (64).

Brierly and Settlemire found that the accumulation of K^{+} by beef heart mitochondria, in vitro, is markedly stimulated by the addition of Zn^{++} (as zinc acetate). The observed accumulation is accompanied by increased respiration and extensive reversible swelling of the mitochondria. They found that the accumulation is inhibited by zinc chelators and that in the absence of added K^{+} zinc induces a rapid energy-linked expulsion of the endogenous K^{+} of the mitochondria. They concluded that the addition of Zn^{++}, under carefully defined experimental conditions, is sufficient to induce the transport of K^{+} by heart mitochondria (65).

Sadasivan studied the effects of zinc oxide on rats by supplementing their diets with levels of 0.5 and 1.0% for a period of 15 days. He found that urinary excretion of nitrogen is increased at the higher zinc level and that fecal excretion is decreased at both levels. Excretion of phosphorus and sulphur in the urine is decreased at both levels while fecal excretion is simultaneously increased. The retention of all three, N, P, and S, in the body is decreased considerably by the ingestion of zinc oxide. Sadasivan postulated that zinc in some manner affects the assimilation of these constituents in the intestines, so that the reserves in the body are mobilized to maintain their concentration in the body fluids. He suggested that this may be the reason for the retarded growth rate and poor development of the bones of rats fed a diet supplemented with zinc, as has been reported by other workers. He also found that zinc causes an increase in the urinary excretion of both uric acid and creatinine, that this may be due to general wastage, especially of the muscle tissues (494).

The addition of zinc (as zinc oxide) to the diets of rats at levels of 0.5 and 1.0% for a period of 15 days was reported by Sadasivan to produce a decrease in the weight of the liver and of its fat content. On a high-fat, low-protein diet, on which control rats developed fatty liver, these changes were more pronounced. It was suggested that zinc may act as a lipotropic agent. Analysis of the femurs of the rats showed that zinc appreciably reduced the dry weight and ash content of the bones, indicating that the zinc supplement interfered with development and mineralization (496).

According to Sadasivan, the changes in the metabolism of nitrogen, phosphorus and sulphur and in urinary excretion of uric acid and total creatinine in rats fed on a high-fat diet supplemented with zinc (0.5% or 1.0%, as zinc oxide) are similar to those previously reported for a stock diet (See Sadasivan, 494). The 0.5% and 1.0% supplements of zinc caused the activity of intestinal alkaline phosphatase to be lowered and the phosphatase activity of the liver and kidneys to be increased. The fat content of the liver and the assimilation of phosphate from the intestines were lowered by the zinc supplements, but no change in the excretion of fat in the feces was observed (498).

Upon feeding rats 0.4% zinc (as zinc oxide) for 8 weeks, Cox and Harris observed decreases in the concentrations of iron storage proteins (ferritin and hemosiderin) and hemoglobin in the liver. The depletion of ferritin was higher than that of hemosiderin, accounting for 77% of the iron loss (122).

Hagan et al. fed zinc sulfate to weanling rats at 1000, 500, and 100 ppm, and to dogs at 200 mg/kg/day initially, then 100 mg/kg, and finally 50 mg/kg. In the rats they observed microcytosis coupled in some cases with polychromasia and in others with hyperchromasia. No effect on red cell numbers or hemoglobin level was observed and the changes in the blood returned to normal despite continued zinc feedings. They found a myeloid-erythroid ratio average of 1.16 to 1.35 in the bone marrow of the zinc-fed rats in contrast to the value of 2.14 found in the controls. Hypochromic anemia was observed in dogs and slight hyperplasia was found in the bone marrow, with no change in the myeloid-erythroid ratio apparent (236).

Duncan et al. reported that the addition of 1.0% zinc to the diet of rats resulted in a 40% reduction in the hemoglobin level. This effect was more pronounced with a 1.5% zinc supplement. They found that the addition of 0.03% copper to the zinc diet increased the hemoglobin, but to sub-optimal levels (147).

Grant-Frost and Underwood studied the effect on rats of the addition of 0.5% zinc (as zinc oxide) to the diet and the relation of supplemental copper to zinc toxicity. They found that zinc markedly reduced the hemoglobin level, copper retention and body fat content of the rats. The addition of 0.4 mg of copper daily to the diet of the zinc-fed rats was found to maintain the copper contents of blood and tissues at normal levels and to afford considerable protection against the anemia. They concluded that anemia is caused by a zinc-induced copper deficiency in the animals and that the zinc not only profoundly reduces the copper concentrations in the blood and tissues but probably antagonizes absorbed copper at the cellular level (218).

Settlemire and Matrone found that the red blood cells of rats fed a 0.75% zinc diet were irregular in shape and typical of a microcytic-hypochromic cell. They also observed a very definite decrease in osmotic fragility of the red cells. The red blood cell life span of the rats fed the high zinc diet was shortened approximately one-fifth to one-fourth that of the controls. They also found that after injection of ^{59}Fe, the excretion of ^{59}Fe closely follows the pattern observed for control rats during the first 8 days. Thereafter, there is a significant increase in ^{59}Fe excretion in contrast with the decrease observed in the feces of the control animals. The time required to show an increase in ^{59}Fe excretion corresponds to the length of the life span of the red blood cells of these rats. Therefore, the authors suggested that the decrease in body iron levels observed when rats are fed high zinc diets is in part associated with a more rapid turnover of the red blood cells (518).

Smith and Larson found that a level of 0.7% zinc in the diet of rats produced a microcytic and hypochromic anemia in 4 weeks and permitted the rats to live for relatively long periods of time. They found that the feeding of copper along with the zinc maintained the hemoglobin at significantly higher levels and that a mixture of iron, copper, and cobalt essentially maintained hemoglobin at normal levels (537).

Cox and Harris studied the effects of excess dietary zinc (zinc oxide) on iron and copper in tissues of the rat. They found that with accumulation of zinc in the liver there is a marked loss of liver iron. They suggested that the reduction of iron is responsible for the production of the anemic condition, and presumably the depression of the activity of some iron-containing enzymes, associated with zinc toxicosis. They found that a decrease in liver copper may also occur, probably as a result of the reduced liver iron rather than a direct effect of the zinc (121).

Cox et al. studied the effects of zinc on fetal and maternal rats by supplementing the diets of pregnant rats with 0.4% zinc, as zinc oxide. The rats were sacrificed at fetal age 16, 21, or 22 days and subjected to a variety of tests. Liver of fetuses from mothers fed 0.4% Zn contained significantly more total zinc and concentration of zinc than liver of fetuses from mothers fed the basal diet. A significantly higher concentration of zinc, but not total, was found in the body of fetuses from maternal rats fed excess zinc. Total copper and concentration of copper were significantly reduced in liver and body of fetuses from mothers fed 0.4% Zn. Total iron and concentration of iron were significantly lower in the body, but unchanged in the liver, of fetuses from mothers fed excess zinc. Total calcium and concentration of calcium were significantly higher in the liver, but were significantly lower in the body, of fetuses from 0.4% Zn group compared with those from the basal groups. Magnesium concentration only was significantly elevated in liver and body of fetuses from mothers fed 0.4% Zn. No significant differences were found between treatments in the dry matter content of maternal tissues. Significant elevations occurred in total zinc and concentration of zinc in liver, kidneys, and brain of maternal animals fed 0.4% Zn. Total zinc was significantly higher in the thymus of these animals. No change was found in the zinc content of other tissues examined. The liver of maternal animals fed excess zinc contained a significantly lower total copper and concentration of copper than the liver of mothers in the basal groups. Copper was not detected in adrenals, spleen, and thymus of animals from each treatment by the technique employed. Copper was not quantitatively altered in other tissues. No significant change was found in the iron content of tissues of mothers fed 0.4% Zn. Total calcium and concentration of calcium were significantly higher in heart and brain, but significantly reduced in kidneys, of maternal rats fed excess zinc. No change was noted in the calcium content of the other tissues from these mothers. Significant reductions were found for total magnesium and concentration of magnesium in the spleen and for magnesium concentration in kidneys of mothers fed the diet containing additional zinc (123).

Magee and Matrone found that addition of zinc chloride or zinc oxide to the diet of rats, at levels of 0.75 and 1.0% for 5 weeks, caused marked decreases in liver copper, iron and zinc. Results of an isotope experiment using zinc carbonate suggest that zinc interferes with copper metabolism by decreasing the utilization and increasing the excretion of copper in the rat, but apparently has little effect on the absorption of copper. Results of another experiment using zinc carbonate indicate that zinc does not interfere with the absorption of iron, but interferes with the utilization of iron, the method being unknown (358).

Heth and Hoekstra reported that supplementation of the diet of the rat with calcium had a significant effect on the retention of ingested ^{65}Zn. They found that increased dietary calcium both increased the early loss of ^{65}Zn by decreasing ^{65}Zn absorption and decreased the rate of turnover of body ^{65}Zn. The calcium decreased the ^{65}Zn content of the soft tissues as represented by liver, kidney, and muscle and increased it in the bones as represented by the femur (264).

Stewart and Magee reported that a dietary level of 0.75% zinc, as zinc carbonate, resulted in marked decreases in bone calcium and phosphorus levels and marked increases in bone zinc levels in rats after feeding for one week. They found that supplements of calcium and phosphorus alleviated the adverse effects of zinc on the deposition of calcium and phosphorus in the bone and prevented the marked accumulation of zinc in the bones of young rats fed high levels of zinc (554).

Cabell and Earle studied the interaction of zinc (fed at 18 and 42 ppm) with three dietary minerals by feeding rats calcium (0.3 and 1.2%), phosphorus (0.3 and 1.2%), and potassium (0.1 and 0.9%). They found that high calcium and high phosphorus independently increase the dietary requirement for zinc, causing a conditioned zinc deficiency and that this effect is additive. Potassium did not increase the zinc requirement (77).

Sutton and Nelson found that calcium chloride may entirely inhibit the increase of blood sugar caused by zinc sulfate but has no effect upon the rise in hemoglobin and red blood corpuscles caused by zinc sulfate (568).

In 1960, Forbes postulated that is seems most probable, on the basis of available evidence, that interference in zinc function by calcium occurs at the cellular level (192).

It has been suggested that the chemical energy resulting from the breakdown of carbohydrate in muscle is converted to the mechanical energy required for muscle contraction by means of an enzymatic reaction between ATP and myosin, during which ATP is hydrolyzed to ADP and inorganic phosphate. Ziff has reported that in vitro-zinc, as is zinc chloride, is a strong inhibitor of this reaction (642).

Blum reported that low concentarations of Zn^{++} enhance the ATPase activity of myosin while high concentrations are inhibitory. He found that the presence of ATP reduces the degree of inhibition caused by Zn^{++} (57).

Using preparations of rabbit skeletal muscle, Carvalho and Avivi found that zinc substitutes for magnesium in activating the ATPase activity and inducing super precipitation of actomyosin suspensions. They also found that Zn and Mg at low concentrations act synergistically with respect to their activiting effect on the ATPase of actomyosin (88).

Gilmour and Griffiths reported that at $25^{o}C$, Zn^{++} activates myosin ATPase in concentrations up to 1.5×10^{-5} M. Higher concentrations of zinc were found to be inhibitory (208).

In vitro studies by Edman have shown that zinc in the presence of ATP induces relaxation of glycerol-extracted muscle fiber bundles. The isometric relaxation is completely reversible and is obtained even with low concentrations of zinc (0.0125 mM) and ATP (0.08 mM). He has suggested that the relaxing effect is probably dependent upon an accumulation of zinc in the fibre proteins (154, 155, 156).

Van Reen studied the effects of dietary zinc on liver enzymes by supplementing the diets of rats with zinc carbonate to provide zinc levels of 0.3-1.0%. Dietary levels from 0.5 to 0.7% resulted in a marked reduction in liver catalase and cytochrome oxidase activities. The administration of copper along with the zinc resulted in an increase of liver enzyme activities to normal values (595).

Duncan et al., found that the addition of 1.0 or 1.5% zinc to the diet of rats resulted in reduction of the cytochrome oxidase activity. The addition of 0.03% copper to the zinc diet raised the activity to a greater than normal level (147).

Cox et al. (123), and Magee and Matrone (538) also reported reduction of cytochrome oxidase activity in rats fed excess zinc.

The activation of desoxyribonuclease on desoxyribonucleate by Zn++ was studied by Miyaji and Greenstein. They found the optimum effective level to be 0.3 micromoles/micromole of nucleic acid phosphorus (393).

Clark and Porteous reported that zinc can either activate or inhibit alkaline beta-glycerophosphatase, depending upon the concentration. They found that combinations of zinc with magnesium cobalt can restore high activity to the enzyme which has been rendered inactive by dialysis, with zinc alone restoring only a small part of the enzyme activity. The optimum Zn++ concentration is about 0.2-1.0 m-equiv./l. When zinc is present in concentrations above the optimum, strong inhibition of the enzyme is observed (110).

Hove et, al. found that crude intestinal phosphatase activity is increased 40 to 100% by the addition of zinc ions in vitro. Crude kidney and bone phosphatase activities are progressively inhibited by concentrations of zinc of 0.004 to 0.070 mM. The authors noted that this difference in response to zinc can not be considered an indication that intestinal phosphatase is different from the others, since after dialysis all three enzymes showed a marked inhibition by zinc (270).

Zn++ was reported by Moss to competitively inhibit inorganic pyrophosphatase activity when the ion concentration is greater than that of the substrate because of the formation of a Zn++ - pyrophosphate complex. When the concentration of pyrophosphate is increased above that of Zn++, the enzyme activity with the increased free substrate is competitively inhibited by the complex. Orthophosphatase activity is also inhibited by the Zn++ - pyrophosphate complex (405).

Kunkel found that zinc ions in concentrations of 0.02 mM inhibit rat liver and kidney succinoxidase systems by forming an inactive complex with the enzyme. Under conditions which favor oxidative phosphorylation, transitory inhibition by zinc occurs, with a subsequent rise in the rate of oxidation to a level above that of the control. A later fall to a lower level of activity was attributed to the zinc inhibition of other Krebs cycle intermediates, particularly the oxidation of alpha-ketoglutarate and

cycle intermediates, particularly the oxidation of alpha-ketoglutarate and citrate. Kunkel noted that with the exception of succinoxidase, the oxidizing enzymes of rat kidney are more readily inhibited by zinc ions than are those of rat liver (324).

During an 8-week feeding study in which rats were given a diet containing 0.4% zinc (as zinc oxide), Cox and Harris observed a reduction in the activity of the liver xanthine oxidase. After 14 days, a loss in activity of approximately 50% occurred in the liver of the female rats while the male rats exhibited about 70% and 60% reduction after 4 and 7 days, respectively (122).

In a later study, Cox et al., found that the activity of xanthine oxidase was significantly lowered in the heart, but not the liver, of rats fed 0.4% zinc (as zinc oxide) for 22 days. They also noted a significant reduction in the activity of serum ceruloplasmin (123).

Potter and DuBois reported that succinic dehydrogenase is hinibited by zinc (455).

Phosphoglucomutase was found by Sutherland to be inhibited by zinc (567).

The inhibition of human plasmin by zinc was reported by Ronwin (480).

That zinc strongly inhibits prolidase was reported by Smith and Bergman (536).

In studies on fasting rabbits, Sahyun found that the addition of 1.0 mg zinc per 1000 units of insulin does not effect the physiological response to the insulin, while the addition of 2 mg zinc or more produces a pronounced augmentative effect (499).

Scott and Fisher fed cats 0.25 g of zinc oxide daily for one month and then 0.30 g for another 2-3 months. They found that the zinc level of the pancreas and liver of the zinc-fed cats was about 7 and 15 times, respectively, as great as that of the controls. The weight of the liver was unchanged, but the weight of the pancreas was only half that of the controls. Marked fibrotic changes in the pancreas of all the cats on the high-zinc diet were observed (515).

Drinker, et al. reported that the long-continued ingestion of large amounts of zinc leads to fibrotic changes in the pancreas, but in no other tissues of the cat (142).

The effects of emetics on gastric secretion were investigated by Schapiro, et al. in dogs with denervated gastric pouches. They found that the intragastric administration of zinc sulfate (75 mg/kg) caused (within 10-20 min.) salivation, retching, and vomiting that persisted for 15-20 min. Gastric secretion remained unaltered from control values for 45-60 min, after which the gastric volume and the acid concentration increased and remained elevated for 120-180 min. During the first hour of the increase, the gastric volume was elevated 76% and during the second hour 74% above the basal (508).

V. Drug Interaction

No information available.

VI. Consumer Exposure

Information received from the NAS/NRC Questionnaire indicates that the following amounts of zinc compounds were used as food additives in 1970.

Substance	Pounds
Zinc Chloride	0
Zinc Gluconate	0
Zinc Oxide	18
Zinc Stearate	0
Zinc Sulfate	6616

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